Docket No.: 05432/0203291-US0
(PATENT)

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of:
Ask Puschl et al.

Application No.: Not Yet Assigned

Confirmation No.: N/A

Filed: Concurrently Herewith

Art Unit: N/A

For: 4-(2-PHENYLSULFANYL-PHENYL)-PIPERIDINE DERIVATES AS SEROTONIN REUPTAKE INHIBITORS

Examiner: Not Yet Assigned

## AFFIRMATION OF CLAIM FOR PRIORITY

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

Applicant hereby claims priority under 35 U.S.C. 119 based on the following prior foreign application filed in the following country on the date indicated:

| Country | Application No. | Date |
|---|---|---|
| Denmark | PA 2003 00520 | April 4, 2003 |
| U.S. | 60/460,528 | April 4, 2003 |

In support of this claim, attached is Form PCT/IB/304 evidencing receipt of the priority documents on April 21, 2004 during prosecution of International Application No. PCT/DK2004/000244.

Dated: October 3, 2005

Respectfully submitted,

By _____

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PCT/DK 2004/000244



# Kongeriget Danmark

Patent application No.: PA 2003 00520

Date of filing: 04 April 2003

Applicant: (Name and address)
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Title: 4-(2-Phenylsulfanyl-phenyl)-piperidine derivatives as serotonin reuptake inhibitors.

IPC: -

This is to certify that the attached documents are exact copies of the above-mentioned patent application as originally filed.



**Patent- og Varemærkestyrelsen**
Økonomi- og Erhvervsministeriet

23 February 2004

Ella Vang M. Hansen

**PATENT- OG VAREMÆRKESTYRELSEN**

# 4-(2-Phenylsulfanyl-phenyl)-piperidine derivatives as serotonin reuptake inhibitors

The present invention relates to novel compounds which are serotonin reuptake inhibitors and as such effective in the treatment of for example depression and anxiety.

## Background of the invention

Selective serotonin reuptake inhibitors (hereinafter referred to as SSRIs) have become first choice therapeutics in the treatment of depression, certain forms of anxiety and social phobias, because they are effective, well tolerated and have a favourable safety profile compared to the classic tricyclic antidepressants.

However, clinical studies on depression indicate that non-response to SSRIs is substantial, up to 30%. Another, often neglected, factor in antidepressant treatment is compliance, which has a rather profound effect on the patient's motivation to continue pharmacotherapy.

First of all, there is the delay in therapeutic effect of SSRIs. Sometimes symptoms even worsen during the first weeks of treatment. Secondly, sexual dysfunction is a side effect common to all SSRIs. Without addressing these problems, real progress in the pharmacotherapy of depression and anxiety disorders is not likely to happen.

In order to cope with non-response, psychiatrists sometimes make use of augmentation strategies. Augmentation of antidepressant therapy may be accomplished through the co-administration of mood stabilizers such as lithium carbonate or triiodothyronin or by the use of electroshock.

The effect of combined administration of a compound that inhibits serotonin reuptake and a 5-$HT_{1A}$ receptor antagonist has been evaluated in several studies (Innis et al. *Eur. J. Pharmacol.* **1987**, *143*, 1095-204 and Gartside *Br. J. Pharmacol.* **1995**, *115*, 1064-1070, Blier et al. *Trends in Pharmacol. Science* **1994**, *15*, 220). In these studies,

it was found that 5-$HT_{1A}$ receptor antagonists would abolish the initial brake on 5-HT neurotransmission induced by the serotonin reuptake inhibitors and thus produce an immediate boost of 5-HT transmission and a rapid onset of therapeutic action.

Several patent applications have been filed, which cover the use of a combination of a 5-$HT_{1A}$ antagonist and a serotonin reuptake inhibitor for the treatment of depression (see e.g. EP-A2-687472 and EP-A2-714663).

Another approach to increase terminal 5-HT would be through blockade of the 5-$HT_{1B}$ autoreceptor. Microdialysis experiments in rats have indeed shown that increase of hippocampal 5-HT by citalopram is potentiated by GMC 2-29, an experimental 5-$HT_{1B}$ receptor antagonist.

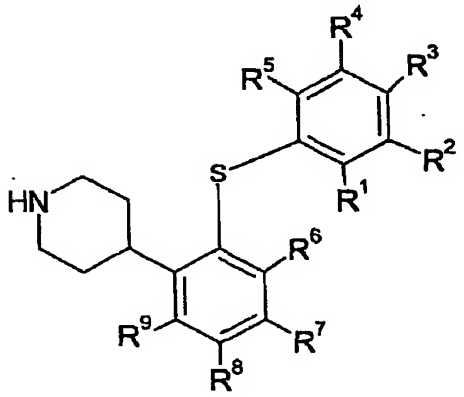
Several patent applications covering the combination of an SSRI and a 5-$HT_{1B}$ antagonist or partial agonist have also been filed (WO 97/28141, WO 96/03400, EP-A-701819 and WO 99/13877).

It has previously been found that the combination of a serotonin reuptake inhibitor with a compound having 5-$HT_{2C}$ antagonistic or inverse agonistic effect (compounds having a negative efficacy at the 5-$HT_{2C}$ receptor) provides a considerable increase in the level of 5-HT in terminal areas, as measured in microdialysis experiments (WO 01/41701). This would imply a shorter onset of antidepressant effect in the clinic and an augmentation or potentiation of the therapeutic effect of the serotonin reuptake inhibitor (SRI).

The present invention provides compounds which are serotonin reuptake inhibitors for the treatment of affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and angoraphobia. Some of the compounds also have a combined effect of serotonin reuptake inhibition and 5-$HT_{2C}$ receptor modulation, which according to WO01/41701 would imply a faster onset of antidepressant activity.

**Summary of the invention**

The present invention provides compounds of the general formula I



(I)

wherein $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, and $R^9$ are as defined below.

The invention provides a compound according to the above for use as a medicament.

The invention provides a pharmaceutical composition comprising a compound according to the above or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

The invention provides the use of a compound according to the above or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and angoraphobia.

The invention provides a method for the treatment of an affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and angoraphobia in a living animal

body, including a human, comprising administering a therapeutically effective amount of a compound according to the above or a pharmaceutically acceptable acid addition salt thereof.

**Definition of substituents**

Halogen means fluoro, chloro, bromo or iodo.

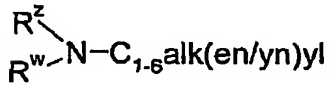
The expression $C_{1-6}$-alk(en/yn)yl means a $C_{1-6}$-alkyl, $C_{2-6}$-alkenyl or a $C_{2-6}$-alkynyl group.

The term $C_{1-6}$ alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, including but not limited to methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl and 2-methyl-1-propyl.

Similarly, $C_{2-6}$ alkenyl and $C_{2-6}$ alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and one triple bond respectively, including but not limited to ethenyl, propenyl, butenyl, ethynyl, propynyl and butynyl.

The terms $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$ alk(en/yn)ylsulfanyl, hydroxy-$C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy-$C_{1-6}$-alk(en/yn)yl and halo-$C_{1-6}$-alk(en/yn)yloxy designate such groups in which the $C_{1-6}$-alk(en/yn)yl are as defined above. Halo means halogen.

$NR^zR^w$-$C_{1-6}$-alk(en/yn)yl designate the group



The term $C_{3-8}$ cycloalkyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, etc.

The term $C_{3-8}$ cycloalkenyl designates a monocyclic or bicyclic carbocycle having three to eight C-atoms and including one double bond.

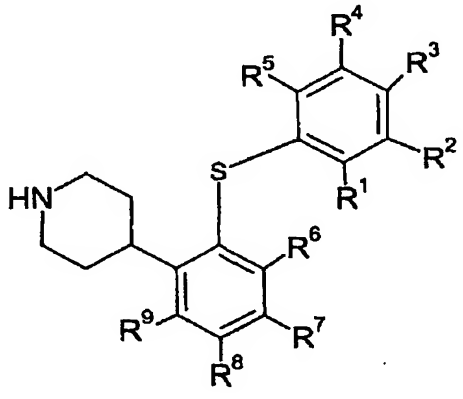
In the term $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl and $C_{1-6}$-alk(en/yn)yl are as defined above.

The term 3-7-membered ring optionally containing one further heteroatom, such as N, O, or S, as used herein refers to ring systems such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, all of which may be further substituted with a group selected from a $C_{1-6}$-alk(en/yn)yl, hydroxy, hydroxy-$C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy-$C_{1-6}$-alk(en/yn)yl.

**Description of the invention**

The present invention relates to 4-(2-phenylsulfanyl-phenyl)-piperidine derivatives which are serotonin reuptake inhibitors and as such effective in the treatment of for example depression and anxiety.

Accordingly the present invention relates to a compound represented by the general formula I




I

wherein

$R^1$, $R^2$, $R^3$, $R^4$, $R^5$ are independently selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-$C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yloxy, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

$R^6$, $R^7$, $R^8$, $R^9$ are independently selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-$C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yloxy, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

provided that at least one of $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, and $R^9$ is different from hydrogen; also provided that when $R^3$ is methyl, then at least one of $R^1$, $R^2$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$ is different from hydrogen;
or a salt thereof.

In one embodiment of the compound of formula I $R^1$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, provided that if one of $R^x$ and $R^y$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl then the other is selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-

alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom. In a further embodiment of the compound of formula I $R^1$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl. In a further embodiment $R^1$ is $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, such as hydrogen, cyanomethyl, $C_{1-6}$-alk(en/yn)yl. In a further embodiment $R^1$ is $NR^xR^y$ wherein $R^x$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, and $R^y$ is selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl. In a further embodiment $R^1$ is $NR^xR^y$ wherein $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom, such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or more selected from a $C_{1-6}$-alk(en/yn)yl, hydroxy, hydroxy-$C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy-$C_{1-6}$-alk(en/yn)yl, e.g. one or two selected from hydroxy, hydroxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyloxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. Typically, $R^1$ is selected from hydrogen; halogen; cyano; $C_{1-6}$-alkyl; $C_{1-6}$-alkyloxy; $C_{1-6}$-alkylsulfanyl; halo-$C_{1-6}$-alkyl; $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alkyl, cyanomethyl; $NR^xR^y$ wherein $R^y$ is selected from hydrogen, or $C_{1-6}$-alkyl, and $R^x$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl wherein $R^z$ and $R^w$ are independently selected from hydrogen, or $C_{1-6}$-alkyl; 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or two selected from hydroxy, hydroxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyloxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. To further illustrate without limiting the invention an embodiment of $R^1$ is hydrogen; another embodiment of $R^1$ is $C_{1-6}$-alkyl, such as methyl; a further embodiment of $R^1$ is halogen, such as fluoro, or chloro.

In a further embodiment of the compound of formula I $R^2$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl. Typically, $R^2$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alkyl, $C_{1-6}$-alkyloxy, $C_{1-6}$-alkylsulfanyl, halo-$C_{1-6}$-alkyl. To further illustrate without limiting the invention an embodiment of $R^2$ is hydrogen; another embodiment of $R^2$ is $C_{1-6}$-alkoxy, such as methoxy.

In a further embodiment of the compound of formula I $R^3$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl. Typically, $R^3$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alkyl, $C_{1-6}$-alkyloxy, $C_{1-6}$-alkylsulfanyl, halo-$C_{1-6}$-alkyl. To further illustrate without limiting the invention an embodiment of $R^3$ is hydrogen; another embodiment of $R^3$ is $C_{1-6}$-alkyl, such as methyl; a further embodiment of $R^3$ is $C_{1-6}$-alkoxy, such as methoxy; a further embodiment of $R^3$ is halogen, such as chloro, or fluoro.

In a further embodiment of the compound of formula I $R^4$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl. Typically, $R^4$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alkyl, $C_{1-6}$-alkyloxy, $C_{1-6}$-alkylsulfanyl, halo-$C_{1-6}$-alkyl. To further illustrate without limiting the invention an embodiment of $R^4$ is hydrogen; another embodiment of $R^4$ is $C_{1-6}$-alkoxy, such as methoxy.

In a further embodiment of the compound of formula I $R^5$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, provided that if one of $R^x$ and $R^y$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl then the other is selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom. In a further embodiment of the

compound of formula I $R^5$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl. In a further embodiment $R^5$ is $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, such as hydrogen, cyanomethyl, $C_{1-6}$-alk(en/yn)yl. In a further embodiment $R^5$ is $NR^xR^y$ wherein $R^x$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, and $R^y$ is selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl. In a further embodiment $R^5$ is $NR^xR^y$ wherein $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom, such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or more selected from a $C_{1-6}$-alk(en/yn)yl, hydroxy, hydroxy-$C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy-$C_{1-6}$-alk(en/yn)yl, e.g. one or two selected from hydroxy, hydroxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyloxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. Typically, $R^5$ is selected from hydrogen; halogen; cyano; $C_{1-6}$-alkyl; $C_{1-6}$-alkyloxy; $C_{1-6}$-alkylsulfanyl; halo-$C_{1-6}$-alkyl; $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alkyl, cyanomethyl; $NR^xR^y$ wherein $R^y$ is selected from hydrogen, or $C_{1-6}$-alkyl, and $R^x$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl wherein $R^z$ and $R^w$ are independently selected from hydrogen, or $C_{1-6}$-alkyl; 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or two selected from hydroxy, hydroxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyloxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. To further illustrate without limiting the invention an embodiment of $R^5$ is hydrogen; another embodiment of $R^5$ is $C_{1-6}$-alkyl, such as methyl; a further embodiment of $R^5$ is halogen, such as chloro, or fluoro.

In a further embodiment of the compound of formula I $R^6$ is selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl. Typically, $R^6$ is selected from hydrogen, halogen, $C_{1-6}$-alkyl, halo-$C_{1-6}$-alkyl. To further illustrate without limiting

the invention an embodiment of $R^6$ is hydrogen; another embodiment of $R^6$ is halogen, such as fluoro.

In a further embodiment of the compound of formula I $R^7$ is selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl. Typically, $R^7$ is selected from hydrogen, halogen, $C_{1-6}$-alkyl, halo-$C_{1-6}$-alkyl. To further illustrate without limiting the invention an embodiment of $R^7$ is hydrogen; another embodiment of $R^7$ is halogen, such as fluoro.

In a further embodiment of the compound of formula I $R^8$ is selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, provided that if one of $R^x$ and $R^y$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl then the other is selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom. In a further embodiment of the compound of formula I $R^8$ is selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl. In a further embodiment $R^8$ is $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, such as hydrogen, cyanomethyl, $C_{1-6}$-alk(en/yn)yl. In a further embodiment $R^8$ is $NR^xR^y$ wherein $R^x$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, and $R^y$ is selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl. In a further embodiment $R^8$ is $NR^xR^y$ wherein $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom, such as 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or more selected from a $C_{1-6}$-alk(en/yn)yl, hydroxy,

hydroxy-$C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy-$C_{1-6}$-alk(en/yn)yl, e.g. one or two selected from hydroxy, hydroxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyloxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. Typically, $R^8$ is selected from hydrogen; halogen; cyano; $C_{1-6}$-alkyl; $C_{1-6}$-alkyloxy; $C_{1-6}$-alkylsulfanyl; halo-$C_{1-6}$-alkyl; $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alkyl, cyanomethyl; $NR^xR^y$ wherein $R^y$ is selected from hydrogen, or $C_{1-6}$-alkyl, and $R^x$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl wherein $R^z$ and $R^w$ are independently selected from hydrogen, or $C_{1-6}$-alkyl; 1-morpholinyl, 1-piperidinyl, 1-azepinyl, 1-piperazinyl, 1-homopiperazinyl, 1-imidazolyl, 1-pyrrolidinyl, 1-azetidinyl, 1-pyrrolyl or pyrazolyl, optionally substituted with one or two selected from hydroxy, hydroxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyloxy-$C_{1-6}$-alkyl, $C_{1-6}$-alkyl, in particular one or two selected from hydroxy, methoxy-methyl, methyl. To further illustrate without limiting the invention an embodiment of $R^8$ is hydrogen; another embodiment of $R^8$ is halogen, such as fluoro, or bromo; a further embodiment of $R^8$ is $C_{1-6}$-alkyl, such as methyl; a further embodiment of $R^8$ is halo-$C_{1-6}$-alkyl, such as $CF_3$.

In a further embodiment of the compound of formula I $R^9$ is selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl. Typically, $R^9$ is selected from hydrogen, halogen, $C_{1-6}$-alkyl, halo-$C_{1-6}$-alkyl. To further illustrate without limiting the invention an embodiment of $R^9$ is hydrogen.

Typically, the compound of formula I has at least one substituent in the phenyl ring(s), selected from any one of $R^1$-$R^9$, which is different from hydrogen, such as 1, 2, 3, or 4 substituents in the phenyl ring(s), selected from any one of $R^1$-$R^9$, which is/are different from hydrogen, and the remaining substituents are hydrogen. Thus, in a further embodiment 1 substituent selected from any one of $R^1$-$R^9$, which is different from hydrogen, is present in either of the two phenyl rings, such as 1 substituent selected from $R^1$-$R^5$, or the substituent is selected from $R^6$-$R^9$. In a further embodiment 2 substituents selected from $R^1$-$R^9$, which are different from hydrogen, are present in either of the two phenyl rings, such as 1 substituent selected from $R^1$-$R^5$, and the other selected from $R^6$-$R^9$, or both substituents are selected from $R^1$-$R^5$. In a further embodiment 3 substituents selected from $R^1$-$R^9$, which are different from hydrogen, are present in either of the two phenyl rings, such as 2 substituents selected

from $R^1$-$R^5$, and the last substituent is selected from $R^6$-$R^9$. To illustrate this further without limiting the invention, some typical embodiments are outlined hereafter.

Thus, in a further embodiment of the compound of formula I one substituent is present which is $R^2$ as defined above, except hydrogen. In a further embodiment of the compound of formula I one substituent is present which is $R^3$ as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are present being $R^3$ and $R^8$, wherein $R^3$ and $R^8$ are as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are present being $R^3$ and $R^6$, wherein $R^3$ and $R^6$ are as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are present being $R^3$ and $R^7$, wherein $R^3$ and $R^7$ are as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are present being $R^1$ and $R^3$, wherein $R^1$ and $R^3$ are as defined above, except hydrogen. In a further embodiment of the compound of formula I two substituents are present being $R^2$ and $R^3$, wherein $R^2$ and $R^3$ are as defined above, except hydrogen. In a further embodiment of the compound of formula I three substituents are present being $R^1$, $R^3$ and $R^8$, wherein $R^1$, $R^3$ and $R^8$ are as defined above, except hydrogen.

In a further embodiment of the compound of formula I said compound is selected from

*4-[2-(4-Chloro-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine,*
*4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-piperidine,*
*4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine,*
*4-[2-(4-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine,*
*4-[2-(4-Methoxy-phenylsulfanyl)-4-fluoro-phenyl]-piperidine,*
*4-[2-(4-Methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine,*
*4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine ,*
*4-[2-(2-Methyl-4-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine,*
*4-[2-(4-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine,*
*4-[2-(4-Chloro-phenylsulfanyl)-phenyl]-piperidine,*
*4-[2-(4-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine,*
*4-[2-(4-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine,*

or a pharmaceutically acceptable salt thereof. Each of these compounds is considered a specific embodiment and may be subject to individual claims.

The present invention also comprises salts of the present compounds, typically, pharmaceutically acceptable salts. Such salts include pharmaceutical acceptable acid addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids.

Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, sulfamic, nitric acids and the like. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, itaconic, lactic, methanesulfonic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methane sulfonic, ethanesulfonic, tartaric, ascorbic, pamoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, theophylline acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline and the like.

Examples of metal salts include lithium, sodium, potassium, magnesium salts and the like.

Examples of ammonium and alkylated ammonium salts include ammonium, methyl-, dimethyl-, trimethyl-, ethyl-, hydroxyethyl-, diethyl-, n-butyl-, sec-butyl-, tert-butyl-, tetramethylammonium salts and the like.

Also intended as pharmaceutical acceptable acid addition salts are the hydrates, which the present compounds, are able to form.

Further, the compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and

the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

The compounds of the present invention may have one or more asymmetric centres and it is intended that any optical isomers (i.e. enantiomers or diastereomers), as separated, pure or partially purified optical isomers and any mixtures thereof including racemic mixtures are included within the scope of the invention.

Racemic forms can be resolved into the optical antipodes by known methods, for example; by separation of diastereomeric salts thereof with an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optically active matrix. Racemic compounds of the present invention can also be resolved into their optical antipodes, e.g. by fractional crystallization of d- or l- (tartrates, mandelates or camphorsulphonate) salts. The compounds of the present invention may also be resolved by the formation of diastereomeric derivatives.

Additional methods for the resolution of optical isomers, known to those skilled in the art, may be used. Such methods include those discussed by J. Jaques, A. Collet and S. Wilen in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optically active compounds can also be prepared from optically active starting materials, or by stereo selective synthesis.

Furthermore, when a double bond or a fully or partially saturated ring system is present in the molecule geometric isomers may be formed. It is intended that any geometric isomers, as separated, pure or partially purified geometric isomers or mixtures thereof are included within the scope of the invention. Likewise, molecules having a bond with restricted rotation may form geometric isomers. These are also intended to be included within the scope of the present invention.

Furthermore, some of the compounds of the present invention may exist in different tautomeric forms and it is intended that any tautomeric forms that the compounds are able to form are included within the scope of the present invention.

The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming pharmacologically active substances. In general, such prodrugs will be functional derivatives of the compounds of the general formula (I), which are readily convertible in vivo into the required compound of the formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

The invention also encompasses active metabolites of the present compounds.

As mentioned above, the compounds of formula I are serotonin reuptake inhibitors, and accordingly may be applicable for the treatment, including prevention, of affective disorders, such as depression, anxiety disorders including general anxiety disorder and panic disorder and obsessive compulsive disorder.

Accordingly, in a further aspect the invention relates to a compound of formula I for use as a medicament.

The present invention also relates to a pharmaceutical composition comprising a compound of formula I and a pharmaceutically acceptable carrier or diluent. The composition may comprise any one of the embodiments of formula I described above.

In an embodiment of the pharmaceutical composition, the compound of formula I is present in an amount of from about 0.001 to about 100 mg/kg body weight per day.

The present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of a disease or disorder, wherein a serotonin reuptake inhibitor is beneficial. The medicament may comprise any one of the embodiments of formula I described above.

In particular the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of affective disorders.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of depression.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of anxiety disorders.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of general anxiety disorder.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of social anxiety disorder.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of post traumatic stress disorder.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of obsessive compulsive disorder.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of panic disorder.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of panic attacks.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of specific phobias.

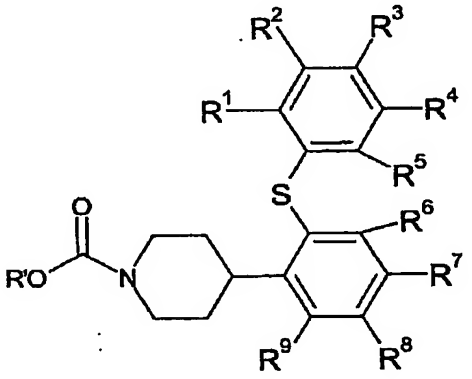
In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of social phobia.

In a further embodiment the present invention also relates to use of a compound of formula I for the preparation of a medicament for the treatment of angoraphobia.

A further aspect of the invention relates to a method for the treatment of a disease or disorder selected from the group consisting of an affective disorder, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and angoraphobia in a living animal body, including a human, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula I.

In a further aspect the present invention relates to a method of preparing a compound of formula I, comprising

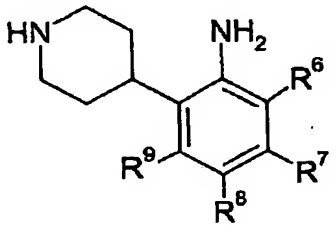
a) Deprotection or cleavage from a polymer support of a compound with formula II



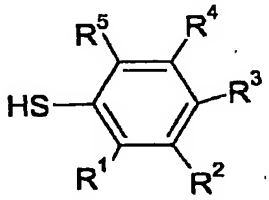
II

wherein $R^1$-$R^9$ are as previously described, and R' is a *tert*-butyl, methyl, ethyl, allyl or benzyl group or R'OCO is a solid supported carbamate group; or

b) Chemical transformation of a compound with formula III to the corresponding diazonium compound and subsequently reacting with a thiophenol of formula IV



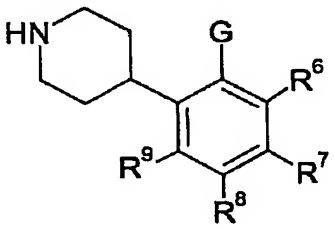

III



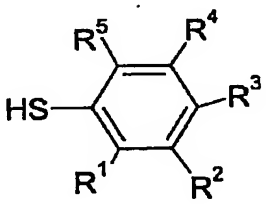

IV

wherein $R^1$-$R^9$ are as previously described; or

c) Reacting a compound of formula V with a thiophenol of formula IV in the presence of a palladium (or copper) catalyst



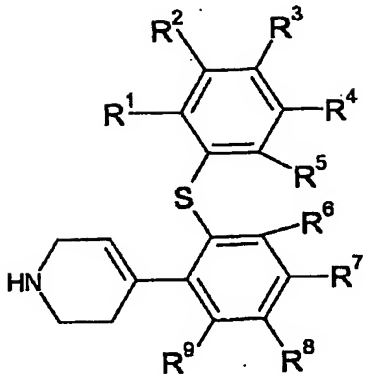

V




IV

wherein $R^1$-$R^9$ are as previously described, and G is a bromine or iodine atom; or

d) Hydrogenate the double bond in a compound of formula VI



VI

wherein $R^1$-$R^9$, are as described above.

**Pharmaceutical compositions**

The compounds of the invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington: The Science and Practice of Pharmacy, 19 Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

Pharmaceutical compositions for oral administration include solid dosage forms such as capsules, tablets, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well known in the art.

Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

Pharmaceutical compositions for parenteral administration include sterile aqueous and nonaqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

Other suitable administration forms include suppositories, sprays, ointments, cremes, gels, inhalants, dermal patches, implants etc.

A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.01 to about 1000 mg, preferably from about 0.05 to about 500 mg, and more preferred from about 0.5 mg to about 200 mg.

For parenteral routes such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. One example is an acid addition salt of a compound having the utility of a free base. When a compound of the formula (I) contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of a free base of the formula (I) with a chemical equivalent of a pharmaceutically acceptable acid. Representative examples are mentioned above.

For parenteral administration, solutions of the novel compounds of the formula (I) in sterile aqueous solution, aqueous propylene glycol, aqueous vitamin E or sesame or peanut oil may be employed. Such aqueous solutions should be suitably buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatine, agar, pectin, acacia, magnesium stearate, stearic acid and lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospho lipids, fatty acids, fatty acid amines, polyoxyethylene and water. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The pharmaceutical compositions formed by combining the novel compounds of the formula (I) and the pharmaceutical acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. Furthermore, the orally available formulations may be in the form of a powder or granules, a solution or suspension in an aqueous or non-aqueous liquid, or an oil-in-water or water-in-oil liquid emulsion.

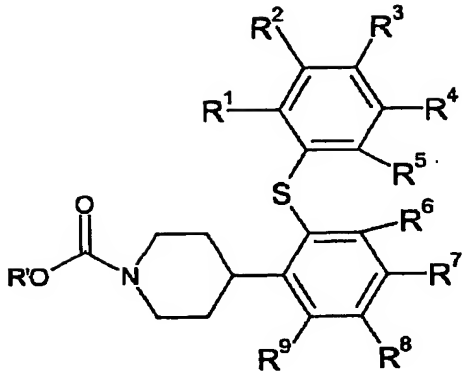
If a solid carrier is used for oral administration, the preparation may be a tablet, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge.

The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g.

If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

The compounds of the invention are prepared by the following general methods:

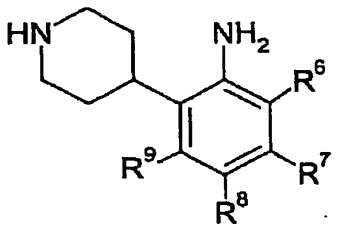
a) Deprotection or cleavage from a polymer support of a compound with formula II



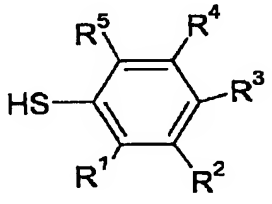
II

wherein $R^1$-$R^9$ are as previously described, and R' is a *tert*-butyl, methyl, ethyl, allyl or benzyl group or R'OCO is a solid supported carbamate group, such as the Wang resin-based carbamate linker.

b) Chemical transformation of a compound with formula III to the corresponding diazonium compound and subsequently reacting with a thiophenol of formula IV



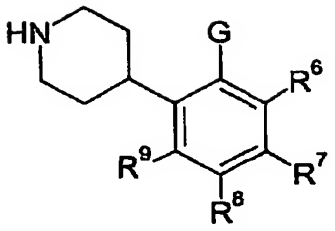
III



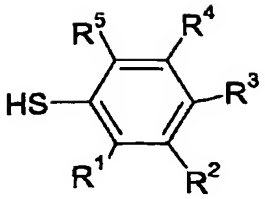
IV

wherein $R^1$-$R^9$ are as previously described.

c) Reacting a compound of formula V with a thiophenol of formula IV in the presence of a palladium (or copper) catalyst



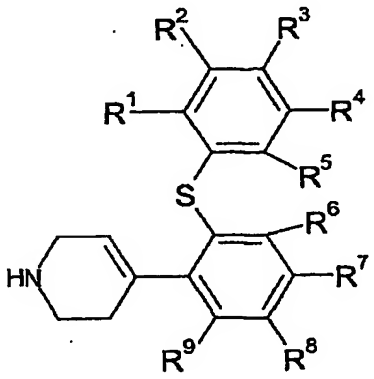
V



IV

wherein $R^1$-$R^9$ are as previously described, and G is a bromine or iodine atom.

d) Hydrogenate the double bond in a compound of formula VI



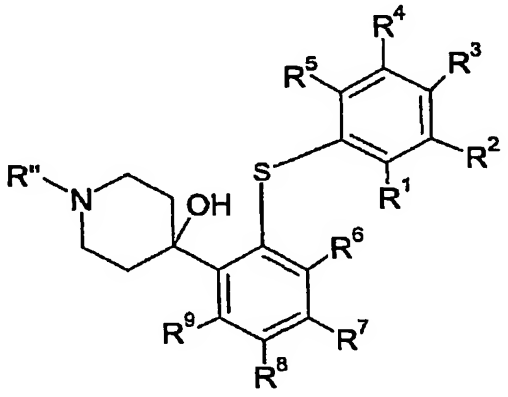
VI

wherein $R^1$-$R^9$, are as described above.

The deprotection according to method a) was performed by standard techniques, known to the persons skilled in the art and detailed in the textbook *Protective Groups in Organic Synthesis* T.W.Greene and P.G.M. Wuts, Wiley Interscience, (1991) ISBN 0471623016. The cleavage from a polymer support, such as from the Wang resin based carbamate linker, according to method a) was performed according to literature

known procedures (Zaragoza *Tetrahedron Lett.* **1995**, *36*, 8677-8678 and Conti et al. *Tetrahedron Lett.* **1997**, *38*, 2915-2918).

Starting materials of formula II in method a) can be prepared by dehydrating a compound of formula VII, and subsequently protecting the amine with e.g. a Boc group, and then reducing the double bond using standard heterogeneous hydrogenation procedures or using homologous hydrogenation procedures such as e.g. Crabtree's catalyst (see e.g Encyclopedia of reagents for organic synthesis, Ed. L. A. Paquette, Wiley (1995), p. 1447.) The dehydration reaction and optional simultaneous deprotection of a compound of formula VII was performed in a similar manner as described in Palmer et al *J. Med. Chem.* **1997**, *40*, 1982-1989. The starting material of formula VII wherein R''=H was prepared from a compound of formula VII wherein R'' is a BOC group (see above) by deprotection with hydrochloric acid in methanol. Compounds of formula VII wherein R = BOC, may be prepared as described in Palmer et al. *J. Med. Chem.* **1997**, *40*, 1982-1989 or the dehydration reaction and optional simultaneous deprotection were performed as described in the experimental procedure below.



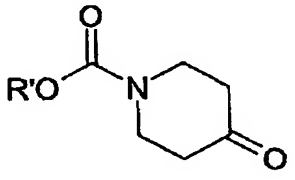

VII

Compounds of formula VII wherein $R^1$-$R^9$ are as previously described, and R'' is either a hydrogen atom or R'' can be a carbamate R'OCO wherein R' is a *tert*-butyl,

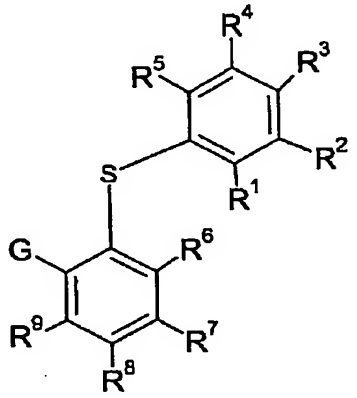
methyl, ethyl, allyl or benzyl group or R'OCO is a solid supported carbamate group, such as the Wang resin-based carbamate linker.

Starting materials of formula II in method a) can also be prepared by removal of the hydroxy group from compounds of formula VII using standard deoxygenation procedures (e.g. Barton reduction). One example of this uses activation with methyl oxalyl chloride followed by reduction with tributyltin hydride and AIBN as described in Hansen et al *Synthesis* **1999**, 1925-1930.

Starting materials of formula VII were prepared from the corresponding properly substituted 1-bromo-phenylsulfanylbenzenes of formula IX by metal-halogen exchange followed by addition of an appropriate electrophile of the formula VIII in a similar manner as described in Palmer et al. *J. Med. Chem.* **1997**, *40*, 1982-1989. Compounds of formula VIII and IX



VIII

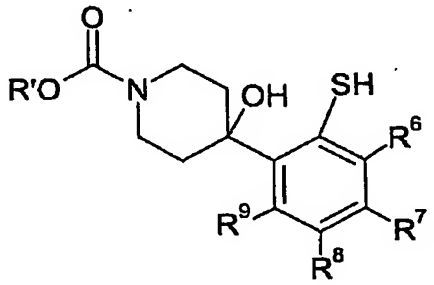


IX

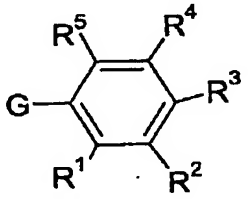
wherein $R^1$-$R^9$ and R' are as previously described, and G is a bromine or iodine atom. The properly substituted 1-bromo-phenylsulfanylbenzenes were prepared in a similar manner as described in the literature by reaction of properly substituted thiophenols with properly substituted aryliodides according to Schopfer and Schlapbach *Tetrahedron* **2001**, *57*, 3069-3073; Bates et al., *Org. Lett.* **2002**, *4*, 2803-2806 and Kwong et al. *Org. Lett.* 2002, *4*, 581-584, as illustrated in the experimental.

Starting material of formula VII can also be prepared by palladium or copper catalysed coupling of a thiophenol of formula X with a compound of formula XI

according to Schopfer and Schlapbach *Tetrahedron* **2001**, *57*, 3069-3073; Bates et al., *Org. Lett.* **2002**, *4*, 2803-2806 or Kwong et al. *Org. Lett.* 2002, *4*, 581-584 . Compound X can be prepared by ortholithiation of a thiophenol derivative of compound IV, or by metal-halogen exchange of a 2-brom-thiophenol derivative, followed by electrophil addition to a compound of formula VIII.



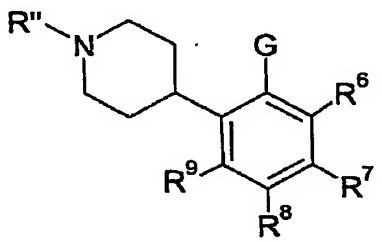
X



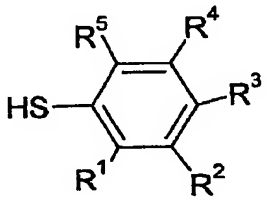
XI

Compounds of formula X and XI wherein $R^1$-$R^9$ and R' are as previously described, and G is a bromine or iodine atom.

Starting materials of formula II in method a) can also be prepared by reacting a compound of formula XII, (R'' is as previously described, G is a bromine or iodine atom, and $R^6$-$R^9$ are as previously described), with a thiophenol of formula IV ($R^1$-$R^5$ are as previously described) in the presence of a palladium or copper catalyst.



XII



IV

Compound XII can be prepared in a similar manner as compound V.

The diazotation followed by reaction with a thiophenol IV according to the method b) was performed by addition of the diazonium salt of the corresponding aniline to a solution of sodium salt of a thiophenol in an aqueous suspension of copper. The starting material of formula III are either commercially available or can be prepared by methods analogues to those described in the literature (e.g. Berridge, M. S. *et al. J. Med. Chem.* **1993**, 36,1284-1290). Thiophenols of the formula IV are either commercially available or can be prepared according to methods described in standard works such as Houben-Weyl, Methoden der organischen Chemie (Methods of Organic Chemistry), Georg-Thieme-Verlag, Stuttgart; Organic Reactions, John Wiley & Sons, Inc. New York, namely under reaction conditions such as those which are known and suitable for such reactions.

The coupling of a compound of formula V with a thiophenol of formula IV according to method c) was performed in the presence of a palladium (or copper) catalyst e.g. by using a method described in Schopfer and Schlapbach *Tetrahedron* **2001**, *57*, 3069-3073; Bates et al., *Org. Lett.* **2002**, *4*, 2803-2806 or Kwong et al. *Org. Lett.* 2002, *4*, 581-584.

Starting materials of formula V in method c) were prepared by diazotation of the corresponding aniline derivative (ref: J. March, Advanced organic chemistry, Wiley (2001) 816) followed by addition of either CuBr or CuI (ref: J. March, Advanced organic chemistry, Wiley (2001) 935-936).

The reduction of the double bond according to method d) was generally performed by catalytic hydrogenation at low pressure (< 3 atm.) in a Parr apparatus. Starting material of formula VI may be prepared from compounds of formula VII.

**Examples**

Analytical LC-MS data were obtained on a PE Sciex API 150EX instrument equipped with IonSpray source and Shimadzu LC-8A/SLC-10A LC system. Column: 30 X 4.6 mm Waters Symmmetry C18 column with 3.5 µm particle size; Solventsystem: A = water/trifluoroacetic acid (100:0.05) and B = water/acetonitrile/trifluoroacetic acid

(5:95:0.03); Method: Linear gradient elution with 90% A to 100% B in 4 min and with a flow rate of 2 mL/min. Purity was determined by integration of the UV (254 nm) and ELSD trace. The retention times (RT) are expressed in minutes. Preparative LC-MS-purification was performed on the same instrument. Column: 50 X 20 mm YMC ODS-A with 5 µm particle size; Method: Linear gradient elution with 80% A to 100% B in 7 min and with a flow rate of 22.7 mL/min. Fraction collection was performed by split-flow MS detection.

$^1$H NMR spectra were recorded at 500.13 MHz on a Bruker Avance DRX500 instrument or at 250.13 MHz on a Bruker AC 250 instrument. Chloroform (99.8%D) or dimethyl sulfoxide (99.8%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, qui = quintet, h = heptet, dd = double doublet, dt = double triplet, dq = double quartet, tt = triplet of triplets, m = multiplet and b = broad singlet.

**Preparation of Intermediates**

*1-Bromo-2-(4-chloro-phenylsulfanyl)-5-(trifluoromethyl)-benzene*

To a stirred solution of $Pd_2dba_3$ (0.183 g, 0.2 mmol) and bis(2-diphenylphosphinophenyl)ether (DPEphos) (0.215 g, 0.2 mmol) in toluene (80 ml) was added 2-bromo-4-trifluoromethyl-iodbenzene (7.02 g, 20 mmol), 4-chlorothiophenol (2.89 g, 20 mmol) and KOBu$^t$ (2.46 g, 22 mmol) at room temperature (rt). The reaction mixture was stirred for 2.5 h at 100 C and then cooled to rt and filtered through celite. The solvent was evaporated off and the crude product was purified by flash chromatography on silica gel (eluent: AcOEt/heptane 20:80) to produce the intermediate as an oil. LC/MS (m/z) 365.9 ($MH^+$); RT = 4.68 min; purity (UV, ELSD): 84%, 99%; yield: 4.53 g (81%).

The following intermediates for **1b-1j** and **2a-2b** were prepared analogously:

*1-Bromo-2-(4-methoxy-phenylsulfanyl)-benzene (CAS 15861-50-4)*

*(intermediate for 1b)* LC/MS (m/z) 293.7 ($MH^+$); RT = 3.99; purity (UV, ELSD): 85%, 100%; yield: 4.66 g (97%).

*1-Bromo-2-(2,4-dimethyl-phenylsulfanyl)-5-(trifluoromethyl)-benzene*

*(intermediate for 1c)* GC/MS (m/z) 362 ($MH^+$); RT = 12.13; purity: 87%; yield: 2.92 g (81%).

*1-Bromo-2-(4-chloro-phenylsulfanyl)-4-fluoro-benzene*

*(intermediate for 1d)* LC/MS (m/z) 317.9 ($MH^+$); RT = 4.37; purity (UV, ELSD): 95%, 98%; yield: 2.66 g (84%).

*1-Bromo-2-(4-methoxy-phenylsulfanyl)-4-fluoro-benzene*

*(intermediate for 1e)* LC/MS (m/z) 314.0 ($MH^+$); RT = 4.03; purity (UV, ELSD): 81%, 85%; yield: 2.57 g (82%).

*1-Bromo-2-(4-methyl-phenylsulfanyl)-5-methyl-benzene*

*(intermediate for 1f)* LC/MS (m/z) 293.9 ($MH^+$); RT = 4.45; purity (UV, ELSD): 95%, 99%; yield: 2.45 g (84%).

*1-Bromo-2-(2,4-dimethyl-phenylsulfanyl)-5-methyl-benzene*

*(intermediate for 1g)* LC/MS (m/z) 308.0 ($MH^+$); RT = 4.78; purity (UV, ELSD): 99%, 99%; yield: 3.09 g (100%).

*1-Bromo-2-(2-methyl-4-fluoro-phenylsulfanyl)-5-methyl-benzene*

*(intermediate for 1h)* LC/MS (m/z) 310.0 ($MH^+$); RT = 4.45; purity (UV): 87%; yield: 2.30 g (74%).

*1-Bromo-2-(4-methoxy-phenylsulfanyl)-5-methyl-benzene*

*(intermediate for 1i)* LC/MS (m/z) 307.9 ($MH^+$); RT = 4.16; purity (UV, ELSD): 57%, 72%; yield: 2.74 g (89%).

*1-Bromo-2-(4-chloro-phenylsulfanyl)-benzene (CAS 24535-55-5)*

*(intermediate for 2a)* LC/MS (m/z) 299.8 ($MH^+$); RT = 4.37; purity (UV, ELSD): 96%, 100%; yield: 10.39 g (98%).

*1-Bromo-2-(4-methoxyphenylsulfanyl)-5-fluoro-benzene*

*(intermediate for 2b)* LC/MS (m/z) 314.0 ($MH^+$); RT = 4.03; purity (UV, ELSD): 76%, 86%; yield: 32.3 g (100%).

*1-Bromo-2-(4-chloro-phenylsulfanyl)-5-fluoro-benzene*

*(intermediate for 2c)* LC/MS (m/z) 317.9 ($MH^+$); RT = 4.32; purity (UV, ELSD): 83%, 100%; yield: 8.71 g (79%).

**Preparation of further intermediates**

*1-tert-Butoxycarbonyl-4-[2-(4-chlorophenylsulfanyl)-5-trifluoro-methyl-phenyl]-piperidine-4-ol (intermediate for 1a)*

A solution of BuLi (2.5 M in hexane, 6.5 ml, 16.2 mmol) was slowly added to a stirred solution of 1-bromo-2-(4-chlorophenylsulfanyl)-5-(trifluoromethyl)benzene (5.96 g, 16.2 mmol) in dry THF (40 ml) under Argon at –78 °C. The solution was stirred for 10 min before 4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (3.23 g, 16.2 mmol) was added in one portion. The solution was allowed to warm up to room temperature and then stirred overnight. Saturated aqueous $NH_4Cl$ (80 ml) was added and the solution was extracted with AcOEt (80 ml). The organic phase was washed

with brine, dried ($MgSO_4$) and the solvent was evaporated off. The crude product was purified by flash chromatography on silica gel (eluent: AcOEt/heptane 20:80) to produce the target compound as a white foam. LC/MS (m/z) 388.1 ($MH^+$-Boc); RT = 4.28; purity (UV, ELSD): 98%, 100%; yield: 4.53 g (57%).

The following intermediates for **1b-1i** and **2a-2c** were prepared analogously:

*1-tert-Butoxycarbonyl-4-[2-(4-methoxy-phenylsulfanyl)-phenyl]-piperidine-4-ol (intermediate for **1b**)* LC/MS (m/z) 298.2 ($MH^+$-Boc-$H_2O$); RT = 3.62; purity (UV, ELSD): 99%, 99%; yield: 4.27 g (73%).

*1-tert-Butoxycarbonyl-4-[2-(2,4-dimethyl-phenylsulfanyl)-5-(trifluoro-methyl-phenyl]-piperidine-4-ol (intermediate for **1c**)* LC/MS (m/z) 382.1 ($MH^+$-Boc); RT = 4.41; purity (UV, ELSD): 92%, 99%; yield: 2.56 g (65%).

*1-tert-Butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine-4-ol (intermediate for **1d**)* LC/MS (m/z) 338.2 ($MH^+$-Boc); RT = 4.03; purity (UV, ELSD): 69%, 93%; yield: 2.52 g (57%).

*1-tert-Butoxycarbonyl-4-[2-(4-methoxy-phenylsulfanyl)-4-fluoro-phenyl]-piperidine-4-ol (intermediate for **1e**)* LC/MS (m/z) 334.2 ($MH^+$-Boc); RT = 3.66; purity (UV, ELSD): 58%, 93%; yield: 2.91 g (58%).

*1-tert-Butoxycarbonyl-4-[2-(4-methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine-4-ol (intermediate for **1f**)* LC/MS (m/z) 314.2 ($MH^+$-Boc); RT = 4.12; purity (UV, ELSD): 96%, 100%; yield: 2.15 g (52%).

*1-tert-Butoxycarbonyl-4-[2-(2,4-dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine-4-ol (intermediate for **1g**)* LC/MS (m/z) 328.1 ($MH^+$-Boc); RT = 4.32; purity (UV, ELSD): 100%, 100%; yield: 3.02 g (70%).

*1-tert-Butoxycarbonyl-4-[2-(2-methyl-4-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine-4-ol (intermediate for **1h**)* LC/MS (m/z) 332.3 ($MH^+$-Boc); RT = 4.09; purity (UV, ELSD): 95%, 100%; yield: 2.31 g (53%).

*1-tert-Butoxycarbonyl-4-[2-(4-methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine-4-ol (intermediate for **1i**)* LC/MS (m/z) 330.1 ($MH^+$-Boc); RT = 3.82; purity (UV, ELSD): 96%, 99%; yield: 2.26 g (49%).

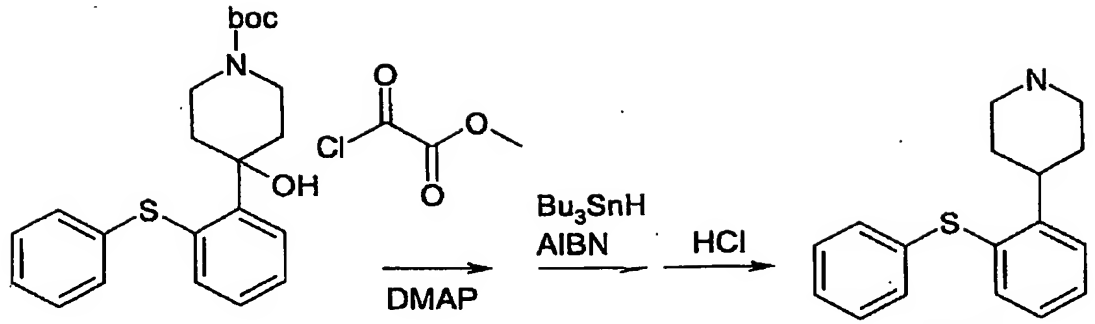
*1-tert-Butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-phenyl]-piperidine-4-ol (intermediate for **2a**)* LC/MS (m/z) 319.9 ($MH^+$-Boc); RT = 3.99; purity (UV, ELSD): 98%, 98%; yield: 12.13 g (83%).

*1-tert-Butoxycarbonyl-4-[2-(4-methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2b**)* LC/MS (m/z) 334.2 ($MH^+$-Boc); RT = 3.66; purity (UV, ELSD): 84%, 98%; yield: 10.35 g (33%).

*1-tert-Butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine-4-ol (intermediate for **2c**)* LC/MS (m/z) 338.2 ($MH^+$-Boc); RT = 4.03; purity (UV, ELSD): 76%, 99%; yield: 5.97 g (50%).

**Compounds of the invention:**

**Method A:**




intermediates for **1a-1i** **1a-1i**

***Example 1***

1a, *4-[2-(4-Chloro-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine fumaric acid*

Methyl Chloro-oxo-acetate (1.37 g, 11.25 mmol) was added to a stirred solution of *1*-tert-butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-5-trifluoro-methyl-phenyl]-piperidine-4-ol (0.98 g, 2.0 mmol) and 4-(dimethylamino)pyridine (0.44 g, 3.6 mmol) in dry $CH_3CN$ (6.4 ml) at 0 °C under argon. The reaction mixture was allowed to reach room temperature and then stirred overnight. Ethyl acetate (40 mL) was added and some salts were removed by filtration through celite. The organic phase was washed with sat. $NaHCO_3$ (40 ml), brine (40 mL) and dried ($MgSO_4$). The solvents were evaporated off and the crude material was dried *in vacuo*. This material was dissolved in dry toluen (13 mL) under argon. $Bu_3SnH$ (0.81 g, 3.0 mmol) and AIBN (82 mg, 0.5 mmol) were added. The solution was stirred under argon at 90 °C for 3.5 h. The solvent was evaporated, and the crude material was purified by flash chromatography on silicagel (eluent: AcOEt in heptane from 10:90) to produce 4-[2-(4-chloro-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine-1-carboxylic acid tert-butyl ester as a clear oil (0.77 g, 82%). This oil was dissolved in MeOH (8 mL) and HCl in diethylether (8 ml) was added at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The solvent was evaporated off and AcOEt (25 ml) was added. The organic phase was extracted with 2M NaOH (8 ml) and washed with brine, dried ($MgSO_4$) and the solvent was evaporated off. This material (588 mg) was dissolved in AcOEt (2.2 ml) and fumaric acid (183 mg, 1.58 mmol, 1eq) dissolved in hot abs EtOH (4.4 ml) was added. The target compound was

collected as a white solid. M.p 180-182 °C. Calculated for $C_{18}H_{17}F_3NS.C_4H_4O_4$ : C 54.15; H 4.34; N 2.87. Found: C 54.01; H 4.60; N 2.73. LC/MS (m/z) 372.1 ($MH^+$); RT = 2.54; purity (UV, ELSD): 97%, 100%; yield: 0.187 g (19%). $^1$H NMR δ 7.6-7.4 (m, 6H); 7.25 (d, 1H); 6.48 (s, 2H); 3.4-3.3 (m, 3H); 3.0-2.9 (m, 2H); 1.99 (m, 2H); 1.9-1.8 (m, 2H).

The following compunds of the invention **1b-1i** were prepared analogously:

**1b**, *4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-piperidine oxalic acid* was collected as a white solid. LC/MS (m/z) 299.9 ($MH^+$); RT = 2.04; purity (UV, ELSD): 95%, 97%; yield: 0.090 g (10%).

**1c**, *4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine oxalic acid* was collected as a white solid. M.p 224-225 °C. Calculated for $C_{20}H_{22}F_3NS.C_2H_2O_4$ : C 58.01; H 5.31; N 3.08. Found: C 57.91; H 5.41; N 3.04. LC/MS (m/z) 366.2 ($MH^+$); RT = 2.45; purity (UV, ELSD): 97%, 99%; yield: 0.61 g (45%). $^1$H NMR δ 7.5 (m, 2H); 7.40 (d, 1H); 7.30 (s, 1H); 7.16 (d, 1H); 6.74 (d, 1H); 3.40 (m, 3H); 3.10 (m, 2H); 2.34 (s, 3H); 2.27 (s, 3H); 2.0 (m, 4H).

**1d**, *4-[2-(4-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine oxalic acid* was collected as a white solid. M.p 191-193 °C. Calculated for $C_{17}H_{17}ClFNS.C_2H_2O_4$ : C 55.40; H 4.66; N 3.40. Found: C 55.21; H 5.17; N 3.11. LC/MS (m/z) 322.1 ($MH^+$); RT = 2.33; purity (UV, ELSD): 83%, 97%; yield: 0.385 g (51%).

**1e**, *4-[2-(4-Methoxy-phenylsulfanyl)-4-fluoro-phenyl]-piperidine hydrochloric acid* was collected as a white solid. M.p 216-218 °C. Calculated for $C_{18}H_{20}FNSO.HCl$ : C 61.09; H 5.99; N 3.96. Found: C 60.21; H 6.26; N 3.71. LC/MS (m/z) 318.1 ($MH^+$); RT = 2.12; purity (UV, ELSD): 96%, 99%; yield: 0.308 g (30%). $^1$H NMR δ 8.90 (br. s, 2H); 7.46 (d, 2H); 7.28 (m, 1H); 7.06 (m, 3H); 6.54 (d, 1H); 3.81 (s, 3H); 3.4-3.25 (m, 3H); 3.05 (m, 2H); 1.88 (m, 4H).

**1f**, *4-[2-(4-Methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine oxalic acid* was collected as a white solid. M.p 166-167 °C. Calculated for $C_{19}H_{23}NS.C_2H_2O_4.0.5H_2O$:

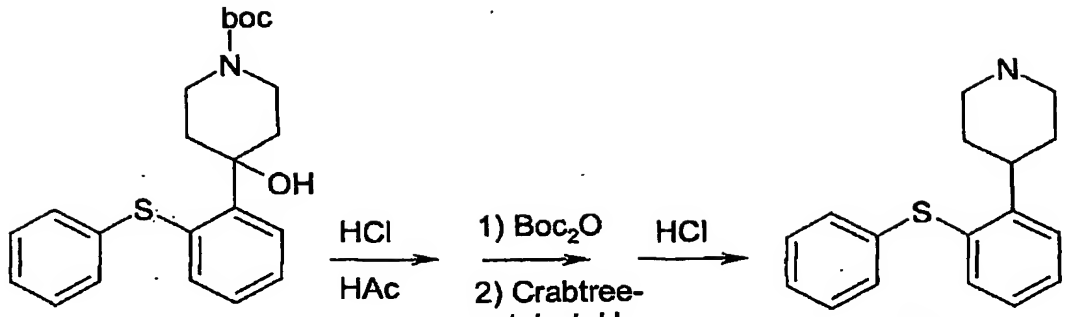
C 63.61; H 6.62; N 3.53. Found: C 63.86; H 6.80; N 3.44. LC/MS (m/z) 298.2 ($MH^+$); RT = 2.29; purity (UV, ELSD): 98%, 99%; yield: 0.233 g (33%). $^1$H NMR δ 7.20-7.04 (m, 7H); 3.40-3.30 (m, 3H); 2.95 (m, 2H); 2.32 (s, 3H); 2.28 (s, 3H); 1.84 (m, 2H); 1.72 (m, 2H).

**1g**, *4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine oxalic acid* was collected as a white solid. M.p 193-194 °C. Calculated for $C_{20}H_{25}NS.C_2H_2O_4$.: C 65.81; H 6.79; N 3.49. Found: C 65.23; H 6.89; N 3.35. LC/MS (m/z) 312.0 ($MH^+$); RT = 2.41; purity (UV, ELSD): 98%, 100%; yield: 0.233 g (33%). $^1$H NMR δ 7.12 (d, 2H); 6.98 (m, 2H); 6.92 (d, 1H); 6.89 (d, 1H); 3.38-3.30 (m, 3H); 2.98 (m, 2H); 2.30 (s, 3H); 2.28 (s, 3H); 2.27 (s, 3H); 1.90-1.80 (m, 4H).

**1h**, *4-[2-(2-Methyl-4-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine oxalic acid* was collected as a white solid. M.p 196-197 °C. Calculated for $C_{19}H_{22}FNS.C_2H_2O_4$.: C 62.20; H 5.98; N 3.46. Found: C 62.00; H 6.16; N 3.38. LC/MS (m/z) 316.0 ($MH^+$); RT = 2.33; purity (UV, ELSD): 96%, 100%; yield: 0.336 g (34%). $^1$H NMR δ 7.22 (d, 1H); 7.15 (s, 1H); 7.06 (m, 3H); 6.97 (d, 1H); 3.40-3.28 (m, 3H); 3.00-2.95 (m, 2H); 2.34 (s, 3H); 2.33 (s, 3H); 1.90-1.77 (m, 4H).

**1i**, *4-[2-(4-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine oxalic acid* was collected as a white solid. M.p 152-153 °C. Calculated for $C_{19}H_{23}NOS.C_2H_2O_4$.: C 62.51; H 6.26; N 3.47. Found: C 61.88; H 6.47; N 3.29. LC/MS (m/z) 313.8 ($MH^+$); RT = 2.16; purity (UV, ELSD): 96%, 99%; yield: 0.375 g (34%). $^1$H NMR δ 7.27 (m, 2H); 7.11-6.98 (m, 3H); 6.96 (d, 2H); 3.74 (s, 3H); 3.40-3.32 (m, 3H); 3.00 (m, 2H); 2.27 (s, 3H); 1.87-1.70 (m, 4H).

**Method B:**




intermediates for **2a-c** **2a-c**

**2a**, *4-[2-(4-Chloro-phenylsulfanyl)-phenyl] piperidine oxalic acid*

Concentrated aq hydrochloric acid (150 ml) was added to a stirred solution of 1-tert-butoxycarbonyl-4-[2-(4-chloro-phenylsulfanyl)-phenyl]-piperidine-4-ol (12.13 g, 28.9 mmol) in acetic acid (450 mL). The solution was boiled under reflux overnight, cooled to room temperature and then stirred in an ice bath. An aqueous solution of NaOH (250 mL) was slowly added and the unclear solution was extracted with AcOEt (3 x 450 ml). The combined organic phases were washed with brine, dried ($MgSO_4$) and the solvents evaporated off. The crude material (8.02 g) was dissolved in THF (195 ml) and $Boc_2O$ (6.96 g, 31.9 mmol) and triethylamine (5 ml) were added. The reaction was stirred overnight and then quenched by addition of sat. $NH_4Cl$ (200 ml). The phases were separated and the organic phase was dried ($MgSO_4$) and the solvent was evaporated off. The crude material was purified by chromatography to produce the Boc protected compound as a white solid (5.63 g). This material was dissolved in $CH_2Cl_2$ (130 ml), $H_2$ was bubbled through the solution and Crabtree catalyst (0.495 g, 1.40 mmol) was added and the hydrogenation was continued overnight. The catalyst was filtered off and the crude product was purified by chromatography to produce the intermediate (5.37 g). This material was dissolved in MeOH (70 ml) and HCl in diethylether (67 ml, 2M, 133 mmol) was added and the reaction mixture was stirred overnight. The solvent was evaporated off and 2M NaOH (200 ml), and AcOEt (400 ml) were added. The aq. phase was extracted with more AcOEt (400 ml). The combined organic phases were washed with brine, dried ($MgSO_4$) and the solvent was evaporated off. This material was purified by chromatography to produce the free

base (1.63 g). This material was dissolved in THF at 50 °C and a solution of oxalic acid (0.48 g) in THF was slowly added.

The target compound was collected as a white solid. M.p. 167 °C. Calculated: C 57.94; H 5.12; N 3.56. Found: C 57.76; H 5.32; N 3.43. LC/MS (m/z) 304.0 ($MH^+$); RT = 2.29; purity (UV, ELSD): 96%, 96%; yield: 1.86 g (15%). $^1$H NMR δ 7.47-7.35 (m, 5H); 7.30 (t, 1H); 7.21 (d, 2H); 3.43-3.32 (m, 3H); 2.97 (t, 2H); 1.92-1.84 (m, 2H); 1.77-1.72 (m, 2H).

The following compounds of the invention **2b-2c** were prepared analogously:

**2b**, *4-[2-(4-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid* was collected as a white solid. RT = 2.16; purity (UV, ELSD): 91%, 98%. $^1$H NMR δ 7.33 (d, 2H); 7.20-7.16 (m, 1H); 7.13-7.06 (m, 2H); 6.98 (d, 2H); 3.77 (s, 3H); 3.54-3.35 (m, 3H); 3.05-3.00 (t, 2H); 1.92-1.76 (m, 4H).

**2c**, *4-[2-(4-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine oxalic acid* was collected as a white solid. M.p. 182 °C. LC/MS (m/z) 304.0 ($MH^+$); RT = 2.33; purity (UV, ELSD): 94%, 96%; yield: 0.241 g. $^1$H NMR δ 7.33 (d, 2H); 7.52-7.49 (m, 1H); 7.39(d, 2H); 7.23-7.15 (m, 4H); 3.40 (t, 1H); 3.33 (d, 2H); 2.96 (t, 2H); 1.86 (q, 2H); 1.73 (d, 2H).

**Measurements of [$^3$H]-5-HT uptake into rat cortical synaptosomes.**

Whole brains from male Wistar rats (125-225 g), excluding cerebellum, are homogenized in 0.32 M sucrose supplemented with 1mM nialamid with a glass/teflon homogenizer. The homogenate is centrifuged at 600 x g for 10 min at 4 °C. The pellet is discarded and the supernatant is centrifuged at 20.000 x g for 55 min. The final pellet is homogenized (20 sec) in this assay buffer (0.5 mg original tissue/well). Test compounds (or buffer) and 10 nM [$^3$H]-5-HT are added to 96 well plates and shaken briefly. Composition of assay buffer: 123 mM NaCl, 4.82 mM KCl, 0.973 mM $CaCl_2$, 1.12 mM $MgSO_4$, 12.66 mM $Na_2HPO_4$, 2.97 mM $NaH_2PO_4$, 0.162 mM EDTA, 10 mM glucose and 1 mM ascorbic acid. Buffer is oxygenated with 95% $O_2$/5% $CO_2$ for 10 min at 37 °C and pH is adjusted 7.4. The incubation is started by adding tissue to a final assay volume of 0.2 mL. After 15 min incubation with radioligand at 37 °C, samples are filtered

directly on Unifilter GF/C glass fiber filters (soaked for 1 hour in 0.1% polyethylenimine) under vacuum and immediately washed with 3 x 0.2 ml assay buffer. Non-specific uptake is determined using citalopram (10 µM final concentration). Citalopram is included as reference in all experiments as dose-response curve.

Preferred compounds of the present invention exhibit serotonin reuptake inhibition below 200 nM ($IC_{50}$) in the assay above. More preferred are the compounds which exhibit inhibition below 100 nM and most preferably below 50 nM.

**[$^3$H]Mesulergine binding to 5-$HT_{2C}$ receptors.**

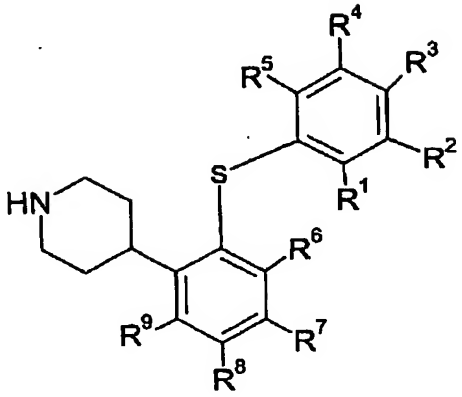
Cell lines expressing 10-20 pmol/mg protein human 5-$HT_{2C}$-vsv receptors (Euroscreen) were harvested in ice-cold 50 mM Tris pH 7.7buffer containing 125 mM NaCl and stored at –80 ° C. On the day of the experiment cells were quickly thawed and homogenized in 50 mM Tris pH 7.7 using an Ultra-Thurax. Aliqouts consisting of 6-30 µg protein, [$^3$H]Mesulergine (1 nM) and testsubstance were incubated for 30 min at 37° C. Total binding was determined using assay buffer (50 mM Tris pH 7.7) and non-specific binding was defined in the presence of 100 µM 5-HT. Bound and free [$^3$H]Mesulergine was separated by vacuum filtration on GF/B filters (pre-soaked in 0.1% PEI for ½ hour) and counted in a scintillation counter.

**5-$HT_{2C}$ receptor efficacy as determined by fluorometry.**

This assay was carried out as described by Porter et al. *British Journal of Pharmacology* **1999**, *128*, 13 with the modifications described below. 2 days before the experiment CHO cells expressing 10-20 pmol/mg protein human 5-$HT_{2C}$-vsv receptors (Euroscreen) were plated at a density sufficient to yield a mono-confluent layer on the day of the experiment. The cells were dye loaded ($Ca^{2+}$-kit from Molecular Devices, and according to their instructions) at 37° C in a 5% $CO_2$ incubator at 95% humidity. Lazer intensity was set to a suitable level to obtain basal values of approximately 8000 RFUs. The variation in basal fluorescence was less than 10%. $EC_{50}$ values were assessed using increasing concentrations of test compound covering 3 decades. $IC_{50}$ values were assessed challenging the $EC_{85}$ of 5-HT with concentrations covering 3 decades of test substances. Ki values were calculated using Cheng-Prusoff equation.

**Claims:**

1. A compound represented by the general formula I



I

Wherein

$R^1$, $R^2$, $R^3$, $R^4$, $R^5$ are independently selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-$C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yloxy, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

$R^6$, $R^7$, $R^8$, $R^9$ are independently selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, hydroxy, hydroxy-$C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yloxy, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-

cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom;

provided that at least one of $R^1$, $R^2$, $R^3$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, and $R^9$ is different from hydrogen; also provided that when $R^3$ is methyl, then at least one of $R^1$, $R^2$, $R^4$, $R^5$, $R^6$, $R^7$, $R^8$, $R^9$ is different from hydrogen;
or a salt thereof.

2. The compound of claim 1, wherein $R^1$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, provided that if one of $R^x$ and $R^y$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl then the other is selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom.

3. The compound of any one of claims 1-2, wherein $R^2$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl.

4. The compound of any one of claims 1-3, wherein $R^3$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl.

5. The compound of any one of claims 1-4 wherein $R^4$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl.

6. The compound of any one of claims 1-5 wherein $R^5$ is selected from hydrogen, halogen, cyano, $C_{1-6}$-alk(en/yn)yl, $C_{1-6}$-alk(en/yn)yloxy, $C_{1-6}$-alk(en/yn)ylsulfanyl, halo-$C_{1-6}$-alk(en/yn)yl, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, provided that if one of $R^x$ and $R^y$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl then the other is selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom.

7. The compound of any one of claims 1-6 wherein $R^6$ is selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl.

8. The compound of any one of claims 1-7 wherein $R^7$ is selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl.

9. The compound of any one of claims 1-8 wherein $R^8$ is selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl, or $NR^xR^y$ wherein $R^x$ and $R^y$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, or $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl, wherein $R^z$ and $R^w$ are independently selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl, provided that if one of $R^x$ and $R^y$ is $NR^zR^w$-$C_{1-6}$-alk(en/yn)yl then the other is selected from hydrogen, $C_{1-6}$-alk(en/yn)yl, cyano-$C_{1-6}$-alk(en/yn)yl, $C_{3-8}$-cycloalk(en)yl, or $C_{3-8}$-cycloalk(en)yl-$C_{1-6}$-alk(en/yn)yl; or $R^x$ and $R^y$ together with the nitrogen to which they are attached form a 3-7-membered ring which optionally contains one further heteroatom.

10. The compound of any one of claims 1-9 wherein $R^9$ is selected from hydrogen, halogen, $C_{1-6}$-alk(en/yn)yl, halo-$C_{1-6}$-alk(en/yn)yl.

11. The compound of claim 1, said compound being

*4-[2-(4-Chloro-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine,*
*4-[2-(4-Methoxy-phenylsulfanyl)-phenyl]-piperidine,*
*4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-trifluoromethyl-phenyl]-piperidine,*
*4-[2-(4-Chloro-phenylsulfanyl)-4-fluoro-phenyl]-piperidine,*
*4-[2-(4-Methoxy-phenylsulfanyl)-4-fluoro-phenyl]-piperidine,*
*4-[2-(4-Methyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine,*
*4-[2-(2,4-Dimethyl-phenylsulfanyl)-5-methyl-phenyl]-piperidine ,*
*4-[2-(2-Methyl-4-fluoro-phenylsulfanyl)-5-methyl-phenyl]-piperidine,*
*4-[2-(4-Methoxy-phenylsulfanyl)-5-methyl-phenyl]-piperidine,*
*4-[2-(4-Chloro-phenylsulfanyl)-phenyl]-piperidine,*
*4-[2-(4-Methoxy-phenylsulfanyl)-5-fluoro-phenyl]-piperidine,*
*4-[2-(4-Chloro-phenylsulfanyl)-5-fluoro-phenyl]-piperidine,*
or a pharmaceutically acceptable salt thereof.

12. A pharmaceutical composition comprising a compound of any one of claims 1-11 or a pharmaceutically acceptable acid addition salt thereof and at least one pharmaceutically acceptable carrier or diluent.

13. The use of a compound of any one of claims 1 to 11 or a pharmaceutically acceptable acid addition salt thereof for the preparation of a medicament for the treatment of affective disorders, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and angoraphobia.

14. A method for the treatment of an affective disorder, such as depression, anxiety disorders including general anxiety disorder, social anxiety disorder, post traumatic stress disorder, obsessive compulsive disorder, panic disorder, panic attacks, specific phobias, social phobia and angoraphobia in a living animal body, including a human, comprising administering a therapeutically effective amount of a compound of any one of claims 1- 11 or a pharmaceutically acceptable acid addition salt thereof.

15. A compound of any one of claims 1-11 for use as a medicament.